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Review article

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Acute kidney injury in patients with burns

Matthieu Legrand[1] ✉, Audra T. Clark[2], Javier A. Neyra[3] & Marlies Ostermann[4]

Abstract

Burn injury is associated with a high risk of acute kidney injury (AKI) with a prevalence of AKI among patients with burns of 9–50%. Despite an improvement in burn injury survival in the past decade, AKI in patients with burns is associated with an extremely poor short-term and long-term prognosis, with a mortality of >80% among those with severe AKI. Factors that contribute to the development of AKI in patients with burns include haemodynamic alterations, burn-induced systemic inflammation and apoptosis, haemolysis, rhabdomyolysis, smoke inhalation injury, drug nephrotoxicity and sepsis. Early and late AKI after burn injury differ in their aetiologies and outcomes. Sepsis is the main driver of late AKI in patients with burns and late AKI has been associated with higher mortality than early AKI. Prevention of early AKI involves correction of hypovolaemia and avoidance of nephrotoxic drugs (for example, hydroxocobalamin), whereas prevention of late AKI involves prevention and early recognition of sepsis as well as avoidance of nephrotoxins. Treatment of AKI in patients with burns remains supportive, including prevention of fluid overload, treatment of electrolyte disturbance and use of kidney replacement therapy when indicated.

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[1]Department of Anaesthesia and Perioperative Care, Division of Critical Care Medicine, University of California San Francisco, San Francisco, CA, USA. [2]Department of General Surgery, Division of Burn, Trauma, Critical Care, University of Texas Southwestern Medical Center, Dallas, TX, USA. [3]Department of Internal Medicine, Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL, USA. [4]Department of Critical Care & Nephrology, King's College London, Guy's & St Thomas' Hospital, London, UK. ✉e-mail: Matthieu.Legrand@ucsf.edu

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Key points

- In patients with burns, acute kidney injury (AKI) is associated with an extremely poor short-term and long-term prognosis.
- Alternative biomarkers of AKI such as cystatin C, proenkephalin and neutrophil gelatinase-associated lipocalin are associated with major adverse kidney events and improve the prediction of AKI.
- Haemodynamic alterations, burn-induced systemic inflammation and apoptosis, haemolysis, rhabdomyolysis, smoke inhalation injury and drug nephrotoxicity are key factors that contribute to AKI in patients with burns.
- Prevention of early AKI mostly involves the correction of hypovolaemia and the avoidance of nephrotoxins such as hydroxocobalamin.
- Sepsis is the main driver of late AKI in patients with burns and early recognition and prevention of sepsis is central to improving outcomes.
- As no specific treatment for burn-induced AKI exists, current treatment remains supportive, including prevention of fluid overload, treatment of electrolytes disturbance and use of kidney replacement therapy when indicated.

Introduction

Burn injury is associated with a high risk of acute kidney injury (AKI). Despite an improvement in survival in the past three decades[1], AKI in patients with burns is associated with an extremely poor short-term and long-term prognosis. Early (within 48 h of burn injury) and late (≥48 h after burn injury) AKI differ in their aetiologies and outcomes. Early AKI is linked to the early phase of burn injury with hypovolaemic shock, haemodynamic alterations, burn-induced inflammation and smoke inhalation, whereas late AKI is associated with drug nephrotoxicity and the development of sepsis. Among patients with burns, late AKI is associated with significantly higher mortality than early AKI or no AKI.

The incidence of AKI and use of kidney replacement therapy (KRT) in patients with burns varies worldwide but >90% of burn injuries occur in low- and middle-income countries[2]. Although burn-associated mortality has more than halved since the 1950s[3], patients remain at a high risk of complications, including multi-organ failure. The development of AKI is associated with increased morbidity and mortality, longer hospital stays and higher health care costs. In low-income countries and conflict settings, patients with burns often receive delayed, inadequate or inappropriate treatment, leading to unnecessary suffering, disfigurement, disability and/or death. The WHO considers burn injuries to be a forgotten global public health crisis[4].

As no specific therapy for AKI in patients with burn injury exists, management focuses on fluid resuscitation and prevention of sepsis and organ failure. However, progress has been made in the discovery of new biomarkers for the early diagnosis of AKI and the identification of AKI subphenotypes. In this Review, we describe the roles of AKI biomarkers in patients with burns, summarize the current understanding of the key pathophysiological processes that lead to AKI in these patients and discuss approaches to prevention and management of AKI in patients with burn injuries. We also highlight the role of artificial intelligence approaches to guide treatment and predict short-term and long-term outcomes of AKI in this high-risk population.

Definitions and biomarkers of AKI

Various definitions have been used to identify AKI in patients with burns, including the Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease criteria, the Acute Kidney Injury Network classification, and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[5]. However, none of these definitions has been specifically validated in patients with burns. The current KDIGO criteria define AKI as an increase in serum creatinine (sCr) of ≥0.3 mg/dl within 48 h or an increase in sCr ≥1.5 times from baseline or urine output (UOP) of <0.5 ml/kg/h for > 6 h[6]. In 2020, the Acute Disease Quality Initiative proposed the integration of novel biomarkers into the definition of AKI[7]. According to the Acute Disease Quality Initiative definition, the presence of plasma or urine biomarkers above specific thresholds are defined as stage 1 AKI, even if the sCr and UOP criteria are not met (that is, subclinical AKI).

Serum creatinine and urine output

A systematic review of 57 studies published between 1960 and 2009 showed that the risk of AKI in patients with burns was very variable with a median prevalence of 14.5% (interquartile range (IQR) 3.3–28.0%)[8]. The median application of KRT was 3.2% (IQR 1.6–11.6%). However, these studies were limited by the use of several different definitions of AKI and the inclusion of heterogeneous burn populations. The highest prevalence of AKI was seen in patients with a burn total body surface area (TBSA) of >60%[9]. Furthermore, the prevalence of AKI may be overestimated or underestimated owing to the limitations of sCr and UOP criteria.

After a decrease in glomerular filtration, the resulting increase in sCr may be delayed as a result of large volume fluid resuscitation and haemodilution[10]. This delay is particularly relevant to patients with burns who often receive large amounts of fluid during the first 24 h after injury. On the other hand, burn injury may be associated with muscle injury and release of creatinine independent of glomerular function. Later in the course of burn injury, detection of AKI can be confounded by sepsis (resulting in a decrease in creatinine production) and loss of muscle mass[10,11]. UOP may be affected by volume depletion, variable osmotic intake, activation of the renin–angiotensin–aldosterone system (RAAS) and increased antidiuretic hormone secretion[12]. Thus, in the early phase of burn injury, UOP may not correlate with glomerular filtration and/or intrinsic kidney damage. Although low UOP is extremely likely to be due to hypovolaemia during the first hours after burn injury[13–15], alternative factors such as microcirculatory dysfunction and tubular cell damage could potentially contribute at a later stage when the systemic inflammatory response predominates and uncoupling of cardiac output and UOP occurs. Recognizing situations in which further fluid resuscitation is unlikely to increase UOP is essential to avoid over-resuscitation and fluid overload. Similarly, lack of an increase in UOP after fluid administration should raise concerns about alternative causes of oliguria and prompt re-evaluation of the need for further fluid therapy.

Alternative biomarkers

In patients with burns, alternative biomarkers of kidney function might detect AKI more reliably than sCr and UOP and differentiate between renal and non-renal causes of changes in sCr (Table 1). Plasma neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of inflammation and tubular injury that has been repeatedly shown to be elevated in patients with burns and is associated with worsening of AKI and risk of

Table 1 | Studies exploring the prognostic and diagnostic values of biomarkers of kidney injury in patients with burns

Study (year)	Population	Biomarkers	Outcomes	Key findings	Ref.
Dépret et al. (2018)	87 patients with burn TBSA > 20%	Plasma NGAL	MAKE, AKI	Plasma NGAL was higher among patients who experienced MAKE than among those who did not meet this end point (423 (IQR: 327–518) pg/ml vs 184 (IQR: 147–220) pg/ml, $P<0.001$); in multivariate analysis, plasma NGAL on admission remained associated with MAKE	17
Dépret et al. (2017)	130 patients with burn TBSA > 20% and/or shock and/or mechanical ventilation at admission	Haptoglobin	MAKE, AKI	Undetectable haptoglobin was associated with MAKE (OR 6.33, 95% CI 2.34–16.45, $P<0.001$) and AKI (OR 8.32, 95% CI 2.86–26.40, $P<0.001$)	61
Yang et al. (2014)	90 patients with burn TBSA ≥ 20%	Cystatin C, plasma and urine NGAL	AKI, mortality	The levels of serum cystatin C and plasma and urine NGAL were associated with AKI; plasma and urine NGAL levels were associated with mortality	18
Sen et al. (2015)	30 adults with burn TBSA > 20%	Whole-blood NGAL	AKI	4 h after injury, NGAL was higher among patients with AKI than among those without AKI (182.67 ± 83.3 vs 107.37 ± 46.15); NGAL was associated with AKI	131
Yavuz et al. (2014)	22 children with burns	Serum and urine NGAL	AKI	Serum and urine NGAL at admission and day 5 were higher in patients with AKI than in those without AKI	132
Kim et al. (2018)	84 patients with burns	Serum cystatin C, serum and urine NGAL	AKI	Median NGAL level increased from admission to day 7	133
Ren et al. (2015)	95 patients with burns	KIM1 and IL-18	AKI	KIM1 and IL-18 levels at admission and 48 h were higher in patients who subsequently developed AKI than in those who did not; both KIM1 and IL-18 increased before sCr	24
Hong et al. (2013)	45 patients with burns	Plasma NGAL	Late AKI (>8 days), mortality	Plasma NGAL at days 3 and 7 was higher in patients who developed AKI than in those who did not; plasma NGAL at day 7 was higher in patients who died than in those who survived (485 ng/ml vs 111 ng/ml, $P=.001$)	134
Cai et al. (2012)	48 adults with burns	Serum cystatin C	AKI	Serum cystatin C-based eGFR was associated with AKI	135
Suresh et al. (2020)	69 adults with burns	NephroCheck	Death or KRT	NephroCheck scores were higher in patients who died or required KRT than in those who did not meet these outcomes; NephroCheck did not outperform sCr for the prediction of these outcomes	27

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KIM1, kidney injury molecule 1; KRT, kidney replacement therapy; MAKE, major adverse kidney event; NGAL, neutrophil gelatinase-associated lipocalin; OR, odds ratio; sCr, serum creatinine; TBSA, total body surface area.

major adverse kidney events (MAKE), which is a composite end point including death, need for KRT and non-recovery of AKI. MAKE is increasingly used as an end point in observational studies and clinical trials as it enables the competing risks of mortality and other outcomes to be taken into account[16]. A study in 87 patients with burns (TBSA 40% (IQR: 30–55%)), reported that higher plasma NGAL levels at admission were associated with increased risk of MAKE at 90 days[17]. The application of NGAL led to reclassification of patients compared with using clinical scores of burn severity such as the abbreviated burn severity index, sequential organ failure assessment and the simplified acute physiology score II.

Another single-centre study that included 90 patients with a burn TBSA of ≥20% reported that the levels of serum cystatin C and plasma and urine NGAL were independently associated with AKI defined by sCr[18]. NGAL and cystatin C were elevated within 3 h of admission, whereas sCr levels started rising after 12 h. Notably, NGAL is not renal-specific and is strongly impacted by systemic inflammation and neutrophil activation[19]. Burn surgical procedures and septic shock are both temporally associated with an increase in plasma NGAL, independent of AKI[20,21].

An artificial-intelligence and machine-learning algorithm that included NGAL, N-terminal B-type natriuretic peptide (NT-proBNP), UOP and sCr was found to accurately predict AKI and worsening renal function (based on the KDIGO definition) after burn injury[22,23]. NGAL had the best receiver operator characteristics (area under the curve (AUC): 0.93, $P = 0.023$) for the prediction of AKI, followed by NT-proBNP (AUC 0.85). However, the AKI predictive capability of NGAL was enhanced when combined with NT-proBNP or sCr. A machine-learning approach that used deep neural network analysis identified a predictive model including NGAL and NT-proBNP that had an accuracy of 92% to predict AKI, with a sensitivity of 91% and specificity of 93%[23].

Among 95 patients with burns, of whom 11% developed AKI, the levels of urinary kidney injury molecule 1 (KIM1) were significantly higher on hospital admission and at 48 h in those who had AKI at 48 h after admission[24]. The levels of both urinary KIM1 and IL-18 increased before a detectable rise in sCr occurred. The combination of KIM1 and IL-18 had a sensitivity of 72.7% and a specificity of 92.8% for the detection of early AKI (defined as an increase in sCr). Use of pro-enkephalin (PenK), a more sensitive biomarker of glomerular filtration than sCr, may overcome some of the limitations of sCr and UOP in evaluating renal function and glomerular filtration[25]. In a single-centre study in severely ill patients with burns, PenK levels on admission were positively associated with an increased risk of MAKE[26].

The levels of cell-cycle arrest markers tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7) have been combined as a urinary biomarker. In a cohort of 69 patients with burns, urinary [TIMP2]•[IGFBP7] was higher in patients who met a composite outcome of death or need for KRT than in those who did not meet this outcome[27].

Proteinuria can be considered an easily accessible and inexpensive biomarker of AKI[7] and is a common feature of burn-induced AKI[28]. Tubular proteinuria results from tubular cell injury, whereas albuminuria results from glomerular injury and increased glomerular capillary permeability. Disruption of the podocyte protein nephrin, which regulates the permeability of the glomerular basement membrane, is believed to underlie albuminuria. The fibres that constitute the slit diaphragms of the glomerular basement membrane are formed largely by the association of extracellular strands of nephrin[29,30]. Nephrin also interacts with other podocyte proteins, including actin fibres that have roles in the cytoskeleton organization of these cells. Plasma from patients with burns and sepsis-induced apoptosis and reduced nephrin expression in cultured human tubular cells and podocytes[31]. Further experimental studies showed that plasma from these patients also altered the distribution of cytoskeleton actin fibres in tubular cells and significantly increased the diffusion of albumin across podocyte monolayers, suggesting increased glomerular permeability. Megalin, an endocytic receptor that has a pivotal role in the normal reabsorption of filtered proteins, is also suspected to contribute to proteinuria after burn injury[32]. Burn injury induces a decrease of megalin expression on tubular cells resulting in the failure of tubular handling of filtered proteins[31].

Outcomes of AKI

AKI has been repeatedly associated with increased morbidity and mortality among patients with burns[33]. A retrospective study in 18,155 patients who were hospitalized with burns reported a diagnosis of AKI (based on International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes) in 4.6% of participants and in 21% of those with TBSA of >20%[34]. Multivariate analysis showed that AKI was associated with an increased risk of hospital mortality (odds ratio (OR) 7.09 (5.45–9.24)) and increased length of hospital stay (OR 1.54 (1.29–1.85)). At 1 year after injury, AKI was independently associated with increased odds of developing severe chronic kidney disease (OR 2.47 (1.53–4.01)), need for chronic dialysis (OR 2.66 (1.45–4.89)), hospital readmission (OR 1.27 (1.05–1.54)) and all-cause mortality (OR 4.60 (3.69–5.75)). A meta-analysis that included 33 observational studies with a total of 8,200 patients with burns who were admitted to the intensive care unit (ICU), reported an incidence of AKI of 38% (95% CI 30–46%); 12% of all participants received KRT (95% CI 8–16%)[5]. Patients with AKI also spent 8.6 (4.0–13.2) days longer in the ICU and had higher mortality than those without AKI (OR 11.3 (7.3–17.4)).

Late AKI seems to have worse outcomes than early AKI. In patients with burns, early AKI usually refers to AKI within 24–48 h after injury. This definition reflects the pathophysiology of AKI in patients with burns; the early phase of AKI is linked to the early phase of burn injury with hypovolaemic shock, whereas late AKI refers to the development of distributive shock following burn injury. This definition also aligns with the criteria for early and late sepsis-associated AKI[35] and delayed recovery from AKI (that is, beyond 48 h)[36]. As discussed above, the prevalence of early AKI is increased when alternative biomarkers of AKI such as KIM1 and IL-18 are used rather than conventional criteria[24].

A study in 637 adults with burns that used KDIGO criteria reported that 36.9% of participants had early AKI (within 3 days of burn injury) and 10% developed late AKI (>3 days after burn injury)[37]. Both 28-day and 90-day mortality were significantly higher in those with late AKI than in those with early AKI (34.9% versus 19.4% ($P = 0.007$) and 57.1% versus 27.4% ($P < 0.0001$), respectively). After adjusting for potential confounding factors of acute illness severity, late AKI was associated with a 34-fold (15.69–73.75) higher risk of death than no AKI. Although severe forms of AKI are still associated with particularly high mortality (>50%), the prognosis of patients with burn injury who require KRT has improved over the past two decades[5,38,39].

Pathophysiology of AKI

The pathophysiology of AKI after burn injury is multifactorial, with several contributing factors that have a varying impact depending on the timing of AKI after burn injury (Fig. 1). Most episodes of AKI develop during the first week after burn injury and are the direct consequence of the initial insult. Burn injury can also trigger subclinical AKI, defined as the presence of detectable damage biomarkers in plasma or urine without changes in sCr or UOP according to the AKI KDIGO criteria. The occurrence of subclinical AKI is associated with a decrease in renal reserve and an increased risk of developing more severe AKI in the case of an additional renal insult, for example, bleeding, sepsis or nephrotoxicity (Fig. 2). Although the severity of the initial insult seems to have a critical role (as reflected by burn TBSA being a major risk factor for AKI), cumulative exposures to nephrotoxic insults are particularly harmful.

Cardiovascular injury

Burn injury is characterized by an early and profound decrease in cardiac output and an increase in systemic and pulmonary vascular resistance in response to hypovolaemia[13,15]. Substantial fluid loss from the burn wound and fluid shifts from the intravascular to the interstitial space as a result of increased vascular permeability lead to intravascular volume depletion, a decrease in venous return and a subsequent decrease in cardiac output[40–42]. In patients who receive appropriate fluid resuscitation, cardiac output is restored earlier than in those who do not receive fluids. In children, delayed fluid resuscitation during the first 2 h after burn injury is associated with an increased risk of organ failure, including AKI, and death[43].

Within 24 h after burn injury, cardiac output increases to a hyperkinetic state with low systemic and pulmonary vascular resistance (Fig. 3), resulting in distributive shock particularly after extensive injury (TBSA > 20%)[40,44]. Renal perfusion may be reduced, both during the early hypovolaemic phase and during the hyperkinetic distributive phase in the context of low systemic vascular resistance and hypotension.

In the distributive phase, vasopressors might be required to maintain adequate renal perfusion. This hyperinflammatory phase resembles the haemodynamic profile of sepsis and may also contribute to cardiovascular injury. Burn injury can induce cardiac inflammation and dysfunction[45–47], endothelial injury, disruption of vascular integrity and increased vascular permeability[40,47]. Although burn injury does not typically induce severe systolic dysfunction in patients without pre-existing cardiac failure, mild alterations of myocardial contractility and relaxation probably occur in most patients. These changes may lead to increased cardiac filling pressures and promoting venous congestion. Elevated central venous pressure leading to increased pressure in the renal veins is a well-identified risk factor for AKI in patients with right-sided heart failure and in critically ill patients with sepsis[48]. Elevated NT-proBNP, a marker of increased filling pressure in

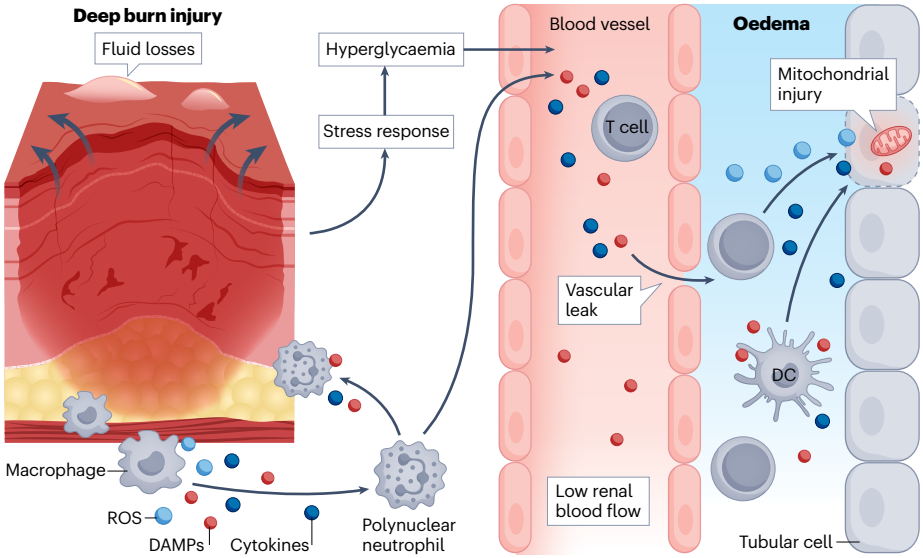

Fig. 1 | Pathophysiology of AKI in patients with burns. After deep burn injury, the release of damage-associated molecular patterns (DAMPs) locally and into the systemic circulation induces local and systemic inflammatory responses. Polymorphonuclear neutrophils contribute to systemic and regional inflammation in burn wounds. Increased vascular permeability induces local and systemic vascular leak and oedema and contributes to a decrease in plasma circulating volume, hypovolaemia and a reduction in renal blood flow. The systemic inflammatory response leads to a second phase of distributive shock and systemic vasodilation. The systemic release of cytokines can also contribute to myocardial injury and cardiac dysfunction (not shown). The systemic stress response induces hyperglycaemia and contributes to tubular injury through mitochondrial dysfunction and oxidative stress. The systemic immune response and oxidative stress are associated with renal microcirculatory dysfunction, tubular injury and tissue oedema, which contribute to cellular damage and acute kidney injury (AKI). DC, dendritic cell; ROS, reactive oxygen species.

the heart, is associated with an increased risk of AKI and progression to severe AKI[23]. The reported values of NT-proBNP in patients with burns are low compared with those in patients with heart failure, but even a small increase in NT-proBNP seems to be associated with an increased risk of AKI. Elevated NT-proBNP in patients with burn injury was also predictive of secondary sepsis, which is a strong contributing factor of late AKI[49].

Activation of the RAAS probably has a role in the cardiovascular response after burn injury. Although the classic RAAS pathway acts in response to hypovolaemia, angiotensin II helps to maintain systemic blood pressure through its vasoconstrictive effect[50,51]. Angiotensin II also acts on the efferent branch of the glomerular vessels and can preserve the glomerular hydrostatic pressure and maintain glomerular filtration. Dipeptidyl peptidase 3 (DPP3) is a predominantly intracellular, ubiquitously expressed metallopeptidase that is involved in the regulation of the RAAS. DPP3 cleaves bioactive peptides, including angiotensin II, and may have a role in the development of vasoplegic shock by reducing angiotensin II levels. DPP3 also cleaves angiotensin (1–7), which has vasodilatory properties and antagonizes the classical RAAS. In a single-centre study including 111 severely ill patients with burns (TBSA > 20%) or needing organ support, the DPP3 plasma level at ICU admission was strongly associated with 90-day mortality, circulatory failure and AKI[52].

Rhabdomyolysis and haemolysis

Deep burn injury can cause direct tissue and muscular oedema, decreased skin compliance and, in some cases, direct muscle thermal injury, resulting in an increased risk of compartment syndrome and rhabdomyolysis. The mechanisms of rhabdomyolysis-induced AKI in patients with burns include myoglobin-induced intratubular cast formation, oxidative stress and accumulation of iron in proximal tubules, leading to intratubular obstruction and proximal tubular cell injury, combined with intravascular hypovolaemia and secondary RAAS activation[53–55]. In patients with suspected compartment syndrome, escharotomy can improve tissue perfusion and minimize muscle damage. This approach is expected to offer nephroprotection in patients with burns[56].

Haemolysis has also been identified as a contributing factor to AKI in severely ill patients with burns. Data from patients after cardiopulmonary bypass show that haemolysis can cause AKI owing to direct tubular toxicity of cell-free haemoglobin (fHb) and renal vasoconstriction and hypoperfusion as a result of nitric oxide (NO) scavenging[57,58]. Haemolysis can occur early after burn injury[59]. As circulating fHb binds to haptoglobin, high circulating fHb or low haptoglobin can generally be considered a biomarker of intravascular haemolysis[57,58,60]. In a single-centre prospective cohort study including 130 severely ill patients with burns (TBSA > 20% and/or with shock and/or requiring mechanical ventilation), 30% had undetectable plasma haptoglobin at ICU admission, which was associated with an increased risk of MAKE (OR 6.33, 95% CI 2.34–16.45, $P < 0.001$) and AKI (OR 8.32, 95% CI 2.86–26.40, $P < 0.001$) after adjusting for potential confounders[61].

Host immune response

Burn injury induces a systemic host response with release of damage-associated molecular pattern (DAMPs)[62]. The white blood cell count and the levels of acute phase proteins (for example, C-reactive

protein and pro-calcitonin) are elevated early after burn injury and associated with a worse prognosis. Burn injury also leads to an increase in inflammation and oxidative stress with a concomitant decrease in antioxidant enzymes, triggering kidney injury. Accumulating evidence suggests that a burst of oxygen free radicals and pro-inflammatory cytokine infiltration leads to cell injury and apoptosis after burn injury and contributes to the development of early AKI[63]. Haem oxygenase 1 (HO-1), an endogenous antioxidant protein, has been reported to protect against burn-induced AKI[64]. Nuclear factor (NF)-κB also seems to have a key role in burn-induced kidney inflammation and subsequent AKI. Antioxidant molecular hydrogen inhibits burn-induced release of inflammatory cytokines in rat kidneys through a NF-κB-mediated signalling pathway, reducing apoptosis and attenuating AKI after burn injury[64]. In a rat model of severe burns, administration of the antioxidant astaxanthin inhibited the MyD88-dependent TLR4–NF-κB pathway and reduced kidney inflammation, apoptosis and kidney damage after burn injury[65]. This study also showed that administration of astaxanthin after burn injury reduced mitochondria-related apoptosis via the PI3K–Akt–Bad pathway.

Hyperglycaemia and mitochondrial dysfunction

Inflammation and mitochondrial dysfunction contribute to alteration of renal perfusion. Burn injury can induce acute stress-related peripheral insulin resistance and a hypercatabolic state that results in secondary hyperglycaemia and kidney mitochondrial dysfunction[66]. In a rabbit model of full thickness 20% TBSA third-degree burn injury and fluid resuscitation, renal dysfunction and histological tubular damage did not correlate with oxygen delivery to the kidney cortex. Renal damage was, however, preceded by a decrease in mitochondrial respiratory chain enzyme activity and was prevented by strict blood glucose control[67]. These data suggest that hyperglycaemia may lead to cytopathic mitochondrial dysfunction, which secondarily contributes to tubular damage. The underlying mechanism is unclear but may involve accumulation of dicarbonyls. These glucose metabolites have a role in tissue injury in hyperglycaemic states through the generation of advanced glycation end products and mitochondrial injury.

Alteration of renal perfusion

Persistent alteration of renal perfusion and tubular cellular injury can occur even when systemic haemodynamics (blood pressure and cardiac output) are restored, owing to dysfunction of the peritubular microcirculation, endothelial damage and intrarenal shunting[68,69]. Ischaemia–reperfusion injury also leads to increased vascular permeability, tissue oedema and increased intra-renal pressure and/or congestion as a consequence of the non-compliant renal capsule. This phenomenon, which has been termed 'renal compartment syndrome', contributes to renal hypoperfusion and tubular injury after ischaemia–reperfusion injury[70]. In a mouse model of renal ischemia–reperfusion, removal of the renal capsule prevented kidney injury and preserved renal function[71]. This experiment highlights the critical role of increased kidney interstitial pressure in response to ischaemia-induced oedema. Fluid overload and right sided cardiac dysfunction may further aggravate the risk of renal congestion after burn injury.

Smoke inhalation injury

Smoke inhalation injury is associated with an increased risk of AKI and mortality in patients with burns[5]. The underlying pathophysiology is not fully understood but is likely to be multifactorial. Inhalation injury is associated with a strong systemic inflammatory response, increased vascular permeability and an increased risk of developing acute respiratory distress syndrome (ARDS)[72]. Hyperinflammatory subphenotypes of ARDS are associated with increased sCr levels. Other non-specific contributors to AKI in patients with ARDS include the haemodynamic impact of positive pressure ventilation (that is, elevated central venous pressure and reduction of cardiac output)[73].

Hydroxocobalamin is commonly used as a prophylactic to treat possible cyanide intoxication after smoke inhalation, but can cause AKI. In a multicentre observational study involving 739 patients with smoke inhalation injury, the use of hydroxocobalamin was associated with an increased risk of AKI, MAKE and death after adjustment for factors of acute illness severity[74]. Mechanisms of kidney toxicity of hydroxocobalamin involve oxaluria and oxalate nephropathy. An observational study in 15 patients with smoke inhalation reported that urine oxaluria was elevated in those who had received hydroxocobalamin compared with those who had not been treated with this agent[75]. Moreover, oxalate nephropathy was observed in kidney biopsy samples from two patients with smoke inhalation injury who had been treated with hydroxocobalamin and developed AKI (Fig. 4). Other studies have reported similar cases[76,77], including patients who did not recover kidney function and required long-term KRT[78]. Non-selective chelation of NO with hydroxocobalamin also results in an increase in blood pressure and is associated with intrarenal vasoconstriction, microvascular dysfunction and renal damage[79], which may contribute to AKI. Thus, we recommend that the use of hydroxocobalamin in patients with burns is restricted to those with a high degree of suspicion of cyanide poisoning (that is, those who were exposed to smoke in a closed space and present with coma, respiratory arrest or haemodynamic instability).

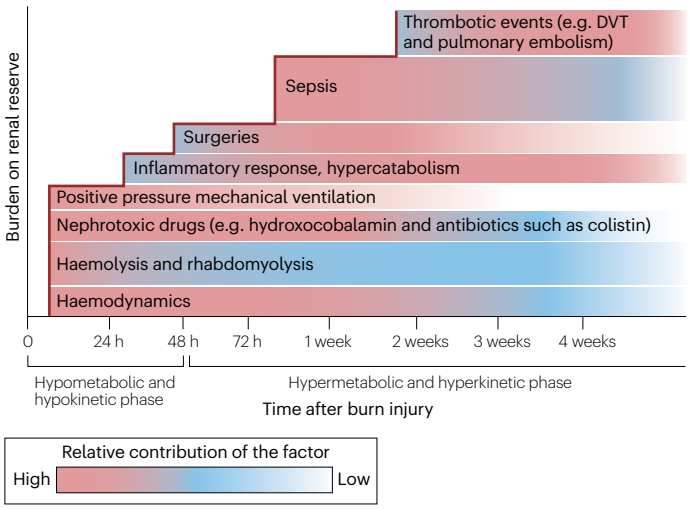

Fig. 2 | Kidney insults and burden on renal reserve after burn injury. After burn injury, patients are exposed to various kidney insults. Haemodynamic compromise during the hypokinetic phase induces renal hypoperfusion. Rhabdomyolysis contributes to kidney damage. During the hypermetabolic phase, systemic and regional inflammation occur. Surgeries can lead to bleeding, the release of damage-associated molecular patterns and inflammation. When sufficient kidney damage occurs, glomerular filtration rate declines and clinical acute kidney injury (AKI) develops. Repeated episodes of kidney damage decrease the renal reserve (that is, the ability of the kidney to tolerate and adapt to stressors) and predispose to more prolonged and severe forms of AKI. DVT, deep vein thrombosis.

Cyanide blocks mitochondrial function by suppressing complex IV of the mitochondrial respiratory chain. As plasma lactate can serve as a surrogate for mitochondrial dysfunction, a plasma lactate of >8 mmol/l is suggestive of cyanide poisoning in patients with smoke inhalation injury[80].

Secondary sepsis

Early sepsis can occur in patients with burn injury, for instance, in the setting of burns combined with penetrating trauma or aspiration pneumonia but is relatively rare. Sepsis is more common later during the course of stay in the ICU (that is, after 7 days) and has been identified as the main risk factor for late AKI[37].

The pathophysiology of sepsis-associated AKI involves haemodynamic alterations, microcirculatory derangements, systemic and regional inflammation and mitochondrial dysfunction[35]. Burn injury-associated AKI shares common pathophysiological processes with sepsis-associated AKI, including induction of renal cell apoptosis and dysfunction. Importantly, the host response to sepsis and the response to burn injury have synergistic effects on renal cell injury. Plasma from patients with burns and sepsis was shown to induce apoptosis of tubular cells[31,63]. Pre-treatment of the plasma with polymyxin B to block lipopolysaccharide (LPS) reduced but did not totally suppress apoptosis, suggesting that additional factors contribute to tubular injury in patients with burns and sepsis[31]. The researchers found that LPS and inflammatory cytokines triggered tubular cell apoptosis by upregulating the expression of Fas and caspase activity. Among patients with burns, the plasma levels of soluble Fas were significantly higher in those who died than in those who survived (3.9 ± 1.8 ng/ml versus 2.6 ± 1.0 ng/ml)[81,82]. The initial severity of the burn injury and the host response are strong risk factors for the subsequent development of sepsis or septic shock. The severity of burn injury, degree of TBSA and concomitant inhalation injury have been repeatedly identified as risk factors for early AKI, whereas the inflammatory response to burn injury predicts the risk of sepsis and late AKI. Immune gene expression analysis of RNA from peripheral blood mononuclear cells revealed that pathways related to IL-10, IL-12, arginase 1 (ARG1) and inducible NO synthase were associated with the risk of infections and mortality[71]. In a single-centre prospective study including 50 patients, early burn injury subphenotypes that are associated with immune and inflammatory responses were associated with risk of septic shock, and high IL-10 levels at admission were associated with mortality[83].

Organ crosstalk

The systemic consequences of burn injury and sepsis trigger multiple organ failure, including AKI. Accumulating evidence suggests that AKI can trigger remote organ injury in the lungs, heart, liver, gut and brain[84–86]. This AKI-induced remote organ injury may therefore contribute to a vicious circle of multiple organ damage and failure. Of note, this evidence is mostly from preclinical models of renal ischaemia–reperfusion or renal obstruction[87,88]. The pathophysiology of organ crosstalk and remote organ injury involves systemic release of cytokines, regional inflammation, apoptosis and the induction of pro-inflammatory and pro-fibrotic pathways. The risk of ARDS and hypoxia is particularly high in patients with burns. In a US cohort of patients with burns, AKI was associated with an increased risk of respiratory failure (OR 2.50 (1.90–3.29)), need for mechanical ventilation (OR 2.41 (1.86–3.12)) and pneumonia (OR 2.39 (1.86–3.05))[34].

The relationship between respiratory distress and AKI is bi-directional. In a single-centre study of 830 patients, those with AKI (48%) were at an increased risk of developing ARDS after adjusting for potential confounders (hazard ratio, 1.73; 95% CI 1.18–2.54), and reciprocally, those with ARDS were at an increased risk of developing AKI (hazard ratio, 1.39; 95% CI 0.99–1.95)[89]. AKI was also associated with an increased risk of cardiovascular injury involving the activation of inflammatory pathways and galectin 3 (Gal-3)[87,90]. Although activation of Gal-3 was reported in critically ill patients, including those with sepsis, the role of Gal-3 in patients with burns needs further research.

Prevention of AKI

Early and appropriate fluid resuscitation is a critical aspect of AKI prevention that improves patient outcomes and so should not be delayed[15]. However, excessive fluid resuscitation has been associated with worse outcomes, including a risk of hypoxia, abdominal compartment syndrome, multiple organ failure and death[91]. Several formulas to predict fluid requirements in patients with burns have been proposed[44]. These formulas provide a rough estimation of fluid requirements at

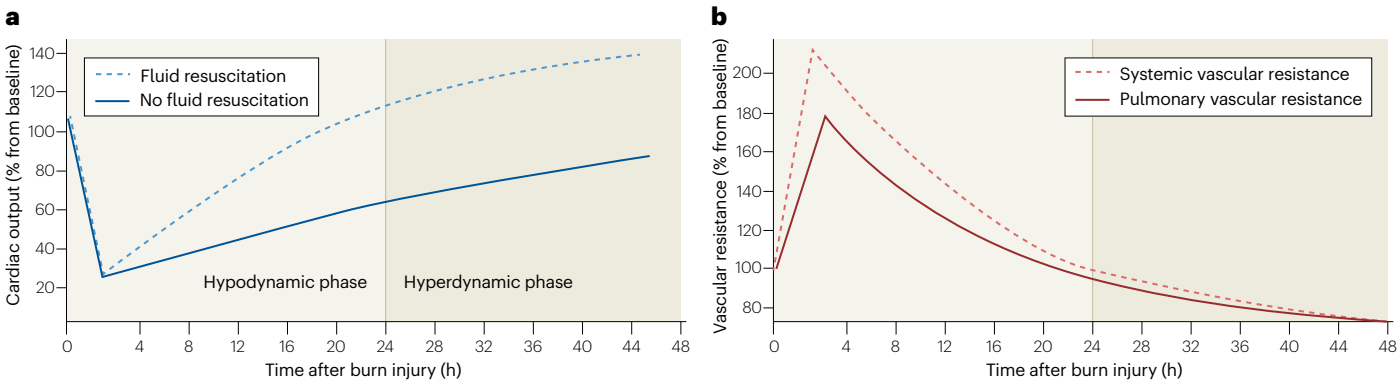

Fig. 3 | Haemodynamic profile and evolution after burn injury. a,**b**, Model figure showing changes in cardiac output with and without fluid resuscitation (**a**) and systemic and pulmonary vascular resistance after burn injury (**b**). Severe burn injury induces capillary leakage and profound hypovolaemia that results in low cardiac output and initial activation of the sympathetic system to preserve the blood pressure. Initial intravascular haemolysis contributes to elevated systemic and pulmonary vascular resistance through chelation of nitric oxide, a potential physiological vasodilator, by free haemoglobin. This phase is associated with initial oliguria. Although the hypercatabolic and inflammatory phase develops, cardiac output increases and vascular resistance decreases, leading to distributive shock. Early fluid resuscitation decreases the duration of hypokinetic shock. Graphs are based on data from a canine model[136].

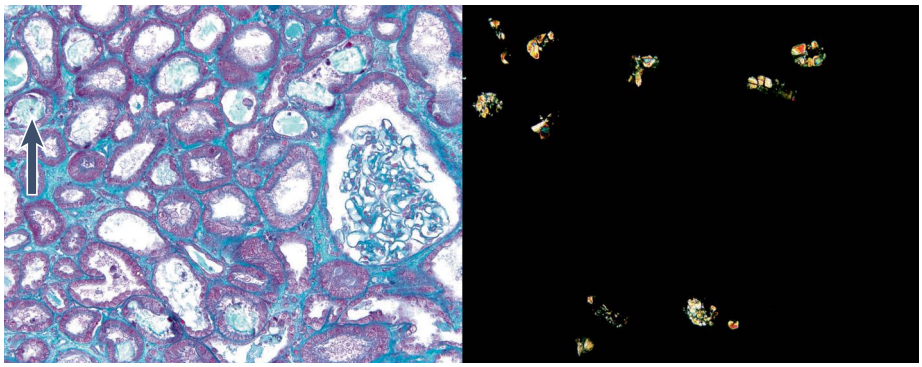

Fig. 4 | Histological findings of oxalate nephropathy in a patient who received hydroxocobalamin after smoke inhalation injury. **a**, Kidney biopsy sample showing calcium oxalate crystals (arrow) in the tubule lumens with mild acute tubular necrosis. **b**, The calcium oxalate crystals appear strongly birefringent under polarized light. Reproduced with permission from ref. 75, Springer Nature Ltd.

the population level but lack precision and individual adjustment is recommended.

Haemodynamic assessment

UOP has long been considered an important physiological target to guide fluid resuscitation in patients with burns. However, UOP has important shortcomings for this purpose; several factors beyond the volaemic status can contribute to an increase (such as osmotic diuresis) or decrease in UOP (such as low solute intake and/or excretion, intrinsic kidney injury with tubular obstruction, intrarenal vasoconstriction, intrarenal compartment syndrome and arginine–vasopressin release)[12]. Nonetheless, during the first 12 h after burn injury, low UOP is extremely likely to be due to hypovolaemia. The contribution of alternative factors (such as ischaemia, inflammation, haemolysis and congestion) increases with worsening systemic inflammatory response at a later stage (after 12–24 h). In patients with no reversal of oliguria despite appropriate fluid resuscitation, careful exploration of the haemodynamic profile is warranted to avoid further unnecessary fluid resuscitation that may lead to fluid overload and harmful consequences. Such investigation should include an assessment of fluid responsiveness using dynamic indices such as pulse pressure variation or stroke volume variations, central venous pressure (as a biomarker of venous congestion) and evaluation of cardiac function using echocardiography. A more detailed discussion and description of haemodynamic management can be found elsewhere[15,44].

Fluid therapy

Historically, the first-line solutions for burn resuscitation have been buffered solutions (such as Ringer's lactate or acetate). The use of NaCl 0.9% has been repeatedly associated with a higher risk of hyperchloraemic metabolic acidosis compared with buffered solutions[92]. Ringer's lactate is also associated with a lower risk of hyperkalaemia than NaCl 0.9%[93]. However, data on clinical outcomes using NaCl 0.9% versus buffered solutions in patients with burns are lacking. A meta-analysis of six randomized controlled trials (RCTs) of intravenous fluid therapy in critically ill adults reported that the risk of death or AKI was lower with use of buffered solutions than with NaCl 0.9%[94]. However, the results are confounded by the fact that patients received relatively low volumes of fluid in these trials. The much larger volumes of crystalloids that are required for burn resuscitation exposes patients to the potential metabolic consequences of NaCl 0.9%. A single-centre RCT in severely ill patients with burns found no difference in acid–base status between those who received Ringer's lactate and those who received Plasmalyte[95]. However, use of Plasmalyte was associated with a higher incidence of hypocalcaemia, probably resulting from accumulation of gluconate in the circulation.

Colloids, particularly albumin, can be used for fluid resuscitation after burn injury. Many centres use albumin combined with crystalloids for the initial phase of burn resuscitation to reduce the volume of crystalloids that is needed, especially in patients with more extensive burn injury (that is, TBSA > 40%) or later in the resuscitation phase after administration of large fluid volumes. The impact of this strategy on renal outcomes is unknown. Likewise, some centres use fresh frozen plasma as colloids in this setting but the evidence to support this practice is very weak[96]. The use of fresh frozen plasma also has some potential risks, especially worsening of lung injury.

As mentioned above, patients with burns tend to need higher volumes of fluid than other critically ill patients, especially during the initial resuscitation phase[15]. This high volume requirement increases the risk of fluid overload and could potentially lead to acute dilution of the sCr concentration, resulting in a delay in AKI diagnosis[97]. Alternative biomarkers of AKI may be particularly useful in this setting.

Computational models and tools

Prediction models with varying degrees of accuracy have been developed to assist physicians with AKI risk assessment in critically ill patients. Furthermore, the number of studies that have applied machine-learning approaches to predict AKI has steadily increased in the past decade[98]. In two cohorts that included a total of 101 patients with burns, machine-learning models that included NGAL and NT-proBNP were shown to predict the development of AKI an average of 62 h before the KDIGO criteria were met[23], potentially enabling an actionable window of interventions to mitigate the risk and reduce the progression of AKI.

Mathematical models have also been developed to predict intravascular fluid volume and UOP after burn injury. A multi-compartmental model that consisted of vascular permeability and intact and burnt tissues was validated in fluid-resuscitated sheep with 40% TBSA. This approach modelled volume kinetics and physiological factors, including glomerular filtration rate modulated by the Starling forces in response to changes in blood volume, and sodium and water reabsorption regulated by antidiuretic hormone[99]. The model showed very good accuracy with a normalized mean absolute error of 17% (IQR of 3) for predicting UOP within 24 h of burn injury.

Several burn centres now use a clinical decision support tool called the Burn Navigator to help to adjust fluid resuscitation. This tool is based on a mathematical fluid model to determine targeted fluid resuscitation infusion rates based on the hourly UOP, burn size, weight of the patient

and time post-injury[100]. Clinicians input the hourly UOP of the patient and the Burn Navigator recommends an intravenous fluid rate for the following hour with the goal of providing the optimal amount of fluid needed to maintain end-organ perfusion and prevent burn shock while minimizing excessive fluid administration. This tool has not yet been validated with respect to its impact on process of care and patient outcomes.

Prevention of secondary sepsis

Patients with burns are at a high risk of secondary sepsis and sepsis is the leading cause of death in these patients[101,102]. According to the Sepsis-3 consensus criteria, sepsis is defined by the presence of a suspected or documented infection and an acute increase in the sequential organ failure assessment score by 2 or more[103]. However, experts recommend that in patients with burns, organ dysfunction during the acute resuscitation phase (the first 3 days after burn injury) should not be considered to be a result of sepsis, given the potential contribution of burn injury to organ failure[103]. This recommendation highlights the similarities in host response between burn injury and sepsis.

Autopsy studies showed that >50% of deaths in patients with burns resulted from infectious complications and sepsis[104,105]. Patients with burn TBSA of >20% are at the highest risk of sepsis, with an incidence of 45%. The skin is the first line of defence against microbial invasion and its loss after burn injury exposes wounds to pathogen colonization and infection. Necrotic tissues (burn eschar) caused by deep partial-thickness or full-thickness burns provide a protein-rich niche for bacterial colonization and proliferation. Lower regional perfusion around burnt tissues (skin and subcutaneous tissues) impairs migration of neutrophils and host immune cells and diffusion of systemically administered antimicrobial agents. The risk of infection is increased further owing to the dysregulated host response in severely ill patients with burns. The function of neutrophils and natural killer cells is impaired after burn injury. Cytokines such as IL-4 and IL-10 inhibit the antigen presentation of macrophages and the bactericidal activity of natural killer cells and neutrophils. Decreased numbers of T lymphocytes and decreased levels of IL-2 and interferon-γ also impair cell-mediated immune responses[62,106].

Pathogenic colonization contributes to the high risk of secondary infections in patients with burns. In a case series of 175 patients with severe burns, a temporal association between organ failure and infections was reported; infection preceded new multiorgan dysfunction in 83% of patients, suggesting a direct role of the host response to infection (that is, sepsis)[101].

Prevention and early recognition of sepsis are critical to avoid late AKI in patients with burns. Strategies to decrease soft-tissue infections include early necrotic tissue removal, use of topical antimicrobial agents and critical care management to support rapid healing through haemodynamic optimization, nutritional support, prevention of thrombotic events and control of the hypermetabolic state using pain control and adjunctive treatments such as propranolol or oxandralone[62]. Application of care bundles to reduce the risk of ventilator-associated pneumonia and catheter-related bloodstream infections is also important[107].

Early excision of necrotic burn tissues in the first few days after burn injury is often considered to limit the ongoing systemic inflammatory response, hypercatabolic state and risk of secondary infections. Evidence of the effectiveness of this approach is, however, limited to small retrospective studies, as prospective studies are lacking[108,109]. The optimal timing of early excision is also still under investigation. Although necessary, surgical excision can induce bleeding, transient bacteraemia and a transient increase in the systemic inflammatory response owing to the release of necrotic debris that act as DAMPs and pathogen-associated molecular patterns in the circulation. Thus, repeated surgery may contribute to the development of late AKI.

Patients with burns are at risk of developing not only bacterial but also fungal and viral infections[110,111]. Early screening for invasive fungal infections (that is, mucormycosis) by detecting circulating DNA decreased the time to treatment and was associated with improved outcomes in patients with severe burns[112]. The use of prophylactic systemic antibiotics in patients with burns is not recommended given the risk of multidrug-resistant bacteria. The impact of perioperative prophylactic antibiotics on sepsis is uncertain and currently under investigation[113]. Importantly, many antibiotics can also be nephrotoxic. β-Lactams can cause acute interstitial nephritis, whereas aminoglycosides and vancomycin increase the risk of acute tubular necrosis[114]. A machine-learning analysis of observational data from a burns unit found that septic shock and the use of intravenous colistin were the primary drivers of an increased incidence of AKI and MAKE during an outbreak of multidrug-resistant *Acinetobacter baumanii*[115].

Diagnostic work-up of AKI

AKI in patients with burns has many aetiologies and contributing factors as discussed above. Haemodynamic assessment (including echocardiography) can rule out a contribution from heart failure and/or fluid shifts; plasma levels of myoglobin and creatine kinase can identify rhabdomyolysis; measurement of fHb and haptoglobin may detect intravascular haemolysis.

Alternative aetiologies of AKI should also be ruled out, especially when AKI develops several days after burn injury. These include drug-induced nephrotoxicity (for example, interstitial nephritis from β-lactams), hypercalcaemia due to prolonged immobilization, and renal obstruction. Sepsis should also be ruled out and appropriate cultures taken. Infection of burn scars and soft tissues is the primary source of sepsis in patients with burns, followed by pneumonia and urinary tract infections.

Treatment of AKI

Treatment of AKI in patients with burns is supportive, including prevention of inadequate and excessive fluid resuscitation, optimization of haemodynamics, treatment of electrolyte and metabolic disorders, and avoidance of superimposed nephrotoxic insults.

Kidney replacement therapy

In general, KRT in patients with burns is considered for those with severe AKI and associated complications, such as severe metabolic acidosis, uraemia, severe electrolyte and metabolic derangements and/or fluid accumulation[116]. A meta-analysis of 57 studies published between 1979 and 2019 that included data on 27,437 patients with severe burns from five continents, reported that the prevalence of AKI was 8.3% and that 37.1% of patients with AKI required KRT (95% CI 29.9–44.2%)[117]. This analysis also showed some regional differences and changes over time. In studies that were published after 2004, only 30% of patients with burns and AKI received KRT. The need for KRT was associated with burn TBSA; 14.7% (95% CI 5.2–24.1) of patients with burn TBSA of >40% received KRT compared with 6.4% (95% CI 4.1–8.7) of those with burn TBSA of <10%.

To date, and to our knowledge, the optimal timing, indications and modality of KRT have not been studied specifically in patients with burns. In the general ICU population, the balance of evidence from clinical trials indicates that immediate initiation of KRT in the absence of a pressing AKI-related emergency does not lead to a

meaningful improvement in clinical outcomes[118]. Moreover, accelerated KRT initiation carries important risks, including hypotension and hypophosphataemia, which are relevant in the context of burn injury. The largest clinical trial of timing of KRT initiation to date, the STARRT-AKI trial, showed that among survivors of AKI, those who were randomly assigned to accelerated initiation of KRT were at a higher risk of being dialysis dependent at 90 days than those who were assigned to a standard KRT initiation strategy (RR 1.74, 95% CI 1.24–2.43)[119].

The current KDIGO consensus recommendation is that KRT should be considered in the case of medically refractory complications ('urgent indications') such as life-threatening hyperkalaemia, pulmonary oedema or uraemic complications[120]. In the absence of urgent indications, deferring KRT appears to be safe in patients who undergo close monitoring of the clinical trajectory, the need for other forms of organ support and the impact of important non-kidney factors ('watch and evaluate approach')[116]. Of note, evidence for the burn injury population is lacking and the criteria for initiating KRT in patients with burns might differ from those for other critically ill populations, especially regarding fluid management in early and late phases of burn injury and solute control, such as elevated blood urea nitrogen in the setting of hypercatabolism.

There is currently no evidence to suggest that when KRT is indicated, any particular modality confers benefit with respect to survival and recovery of kidney function in patients with burns and AKI (Table 2). Thus, general principles for critically ill patients with AKI should apply. Both intermittent and continuous forms of KRT have specific advantages and disadvantages but are generally considered complementary in the critical care setting. A central argument in favour of continuous KRT (CKRT) over intermittent haemodialysis is that CKRT delivers a lower net ultrafiltration rate and is associated with a lower risk of osmotic shifts. For these reasons, CKRT is usually recommended for patients with AKI and haemodynamic instability or with acute brain injury who are at risk of cerebral oedema or with intracranial hypertension[120].

Mortality and long-term kidney outcomes seem to be worse in patients with burns and AKI who are treated with KRT than in patients with burns who do not have AKI. The above-mentioned meta-analysis of 57 studies showed that the mortality of all patients with burns who received KRT was 65.5%[117]. Among patients who survived, 64.1% were dialysis independent, 25% needed temporary dialysis and 10.9% needed dialysis for more than 6 months after hospital discharge. The risk of longer-term dialysis was higher in patients with AKI than in those without AKI. Although specific data for patients with burns are lacking, follow-up by nephrologists has been suggested to improve management and long-term outcomes among patients recovering from AKI[121].

Extracorporeal blood purification

In patients with burn injury, extracorporeal blood purification (EBP) has been suggested as a therapy to remove inflammatory cytokines, prevent a dysregulated immune response, achieve physiological homeostasis and reduce the risk of secondary complications[122,123]. A study in a pig model of burn injury showed substantial removal of IL-1, IL-6, IL-10 and myoglobin when haemoadsorption was performed for 6-h sessions during a 3-day period[124]. However, systemic cytokine and myoglobin concentrations did not change. A meta-analysis that included data from 6 RCTs and an observational study that included a total of 538 patients with burns showed that 28-day mortality was significantly lower among those who received EBP than among those who received conventional treatment (RR = 0.62; 95% CI 0.74 to 0.82; $P = .0009$)[125]. However, no significant differences were reported in body temperature, heart rate, neutrophil count or severe complications between the groups. Furthermore, the studies had substantial heterogeneity regarding the type of EBP used (that is, plasma filtration adsorption, high-volume haemofiltration (HVHF), high-volume haemodiafiltration, haemoperfusion), patient cohorts and timing, dose, frequency and duration of EBP. Thus, the exact role of EBP in the clinical management of patients with burns remains unclear.

Notably, enhanced haemofiltration and adsorption provide clearance of both pro-inflammatory and anti-inflammatory cytokines, which could contribute to immune dysregulation in certain patients at different times during the course of a burn injury. However, the current evidence does not suggest a benefit of HVHF (effluent dose of >50 ml/kg/h for enhanced convective clearance) versus standard-volume haemofiltration in patients with burns. A meta-analysis of studies in patients with sepsis, some of whom had burns, showed that use of HVHF did not improve mortality (OR 0.96 (0.67, 1.38)) or organ failure compared with standard KRT[126]. A small randomized trial in 28 patients with burns suggested a decrease in vasopressor requirements with HVHF compared with standard of care, but no changes in inflammatory markers were detected between the two groups[127].

Table 2 | Characteristics of extracorporeal kidney replacement therapies that can be used for acute support of patients with burn injury

Kidney replacement therapy	Dialysis principle	Blood flow rate (ml/min)	Dialysate flow rate (ml/min)	Replacement fluid rate (ml/min)	Duration (h)	Frequency
Intermittent modalities						
Intermittent haemodialysis	Diffusion	300–400	600–800	0	3–4	3–4 times per week
Sustained low-efficiency dialysis or prolonged intermittent kidney replacement therapy	Diffusion	200–300	200–300	0	6–12	5–7 times per week
Continuous modalities[a]						
Continuous venovenous haemofiltration	Convection	100–300	0	16–50	24	Daily
Continuous venovenous haemodialysis	Diffusion	100–300	16–50	0	24	Daily
Continuous venovenous haemodiafiltration	Diffusion and convection	100–300	16–50	16–50	24	Daily

[a]Continuous kidney replacement therapy modalities may not be available in some hospitals, particularly in low- and middle-income countries.

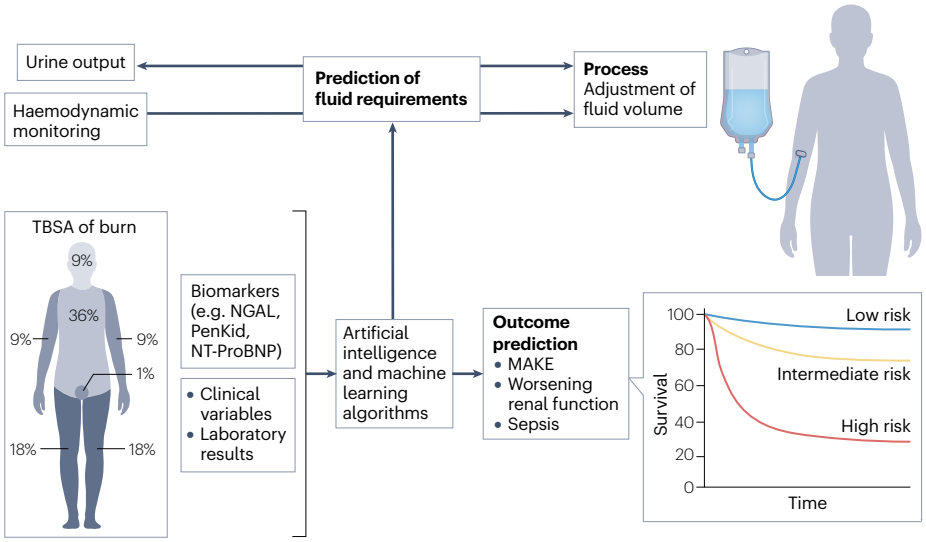

Fig. 5 | Role of biomarkers and artificial intelligence to guide the fluid resuscitation of severely ill patients with burns. Clinical variables (for example, age, sex and medical history), acute kidney injury (AKI) biomarkers and haemodynamic data can be integrated into algorithms that use artificial intelligence for the prediction of renal events and outcomes. Physiological variables such as urine output can also be integrated to guide fluid resuscitation with the aim of preventing AKI and improving outcomes. MAKE, major adverse kidney event; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; TBSA, total body surface area.

Future research directions

To improve the outcomes of patients with burns and AKI, future research should investigate the impact of different haemodynamic management strategies on AKI and global outcomes, including the liberal versus restrictive use of colloids, the use of vasopressors and the use of automated fluid resuscitation strategies. The roles of artificial intelligence, machine learning and novel biomarkers for risk classification, subphenotyping and evaluation of the heterogeneity of treatment effects are also areas of intense research in AKI (Fig. 5).

Identifying subphenotypes of patients with burns that are associated with an increased risk of sepsis is critical for applying targeted strategies for prevention. The identification of biomarkers that are sensitive and specific to sepsis in this population should be a research priority. Specific therapeutic strategies targeting haemolysis and the inflammatory response syndrome should also be tested. For example, novel anti-inflammatory drugs or EBP methods of direct pathogen or endotoxin removal and/or immunomodulation should be evaluated in patients with burn injury developing sepsis complications.

The timing of KRT in patients with burns also deserves further research, as criteria for fluid management and the role of blood urea nitrogen might differ from that of other critically ill patients given fluid creeps (that is, fluid requirements greater than those predicted by standard formulas) and the high catabolism of patients with burns[128]. The best timing for surgical treatment of burns is under investigation, which should provide information on its impact on renal outcomes[129]. Finally, research exploring prediction, prevention and early recognition of sepsis are key to improving outcomes in patients with burns.

Conclusions

In high-income countries, the prognosis of patients with burns has dramatically improved over the past decade, but the incidence of AKI remains high and is associated with poor short-term and long-term outcomes. The severity of the burn injury, the degree of burn TBSA, concomitant smoke inhalation injury and exposure to nephrotoxins (for example, hydroxocobalamin) are risk factors for early AKI, whereas the inflammatory response to burn injury and secondary sepsis are associated with late AKI. The pathophysiology of AKI in patients with burns is multifactorial and current approaches to the prevention and treatment of AKI are supportive, including optimization of fluid management and haemodynamics, treatment of electrolyte and metabolic disorders, avoidance of nephrotoxic exposures, and the prevention of sepsis.

In the future, early recognition and risk classification of AKI (for example, using biomarkers) as well as advances in approaches to AKI prevention (such as using artificial intelligence and machine-learning tools to guide fluid resuscitation) and treatment (including new therapies such as anti-inflammatory medications[130]) are expected to have a major positive impact on the outcomes of patients with burn injuries.

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All authors researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

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